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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,946	03/28/2001	D. Wade Walke	LEX-0157-USA	2952

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LEXICON GENETICS INCORPORATED
8800 TECHNOLOGY FOREST PLACE
THE WOODLANDS, TX 77381-1160

EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 06/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/819,946	Walke et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jan 16, 2001

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-5 is/are pending in the applica

4a) Of the above, claim(s) 4 and 5 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-3 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims 1-5 are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-3, drawn to polynucleotides encoding a polypeptide of SEQ ID NO: 2, classified in class 536, subclass 23.5.

   II. Claim 4, drawn to polynucleotides encoding a polypeptide of SEQ ID NO: 4, classified in class 536, subclass 23.5.

   II. Claim 5, drawn to polynucleotides encoding a polypeptide of SEQ ID NO: 6, classified in class 536, subclass 23.5.

2. The inventions are distinct, each from the other because of the following reasons:

Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to <u>different</u> products, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: Groups I-III are directed to products that are distinct both physically and functionally, and are not required one for the other, and are therefore patentably distinct. Each group represents a chemically distinct group of sequences encoding different proteins, such proteins have not been asserted to have identical functions. Further, a search of one sequence could not be relied upon to provide art that is anticipatory or would render obvious claims

directed to any other group. And to search all three families of sequences in one application would be burdensome

Therefore, because these inventions are distinct for the reasons given above and because a search and examination of all the groups in one patent application would result in an undue burden, since the searches for the groups are not co-extensive, and the subject matter is divergent, restriction for examination purposes as indicated is proper.

3. During a telephone conversation with Peter Seferian on 6/11/02 a provisional election was made to prosecute the invention of Group I, claims 1-3. Affirmation of this election must be made by applicant in replying to this Office action. Claims 4 and 5 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons.

Claim 1 requires a "nucleotide sequence first disclosed in the NHP sequence is SEQ ID NO: 1". Similarly, claim 4 requires contiguous amino acids "first disclosed in the NHP sequence is SEQ ID NO: 2". The phrase "first disclosed" renders the claims indefinite because it is unclear what additional limitations are placed on the claims by the presence of this term, therefore the metes and bounds of the claims cannot be determined.

Claim 2 requires that the nucleic acid hybridize under stringent conditions. The term "stringent conditions" is confusing because it is a relative term and encompasses conditions of varying degrees of stringency - such conditions determining the bounds of the claim. However, the art does not provide an unambiguous definition of the term "stringent conditions" and neither is such a definition given for the term in the specification which puts forth the metes and bounds of the claim Applicant is seeking protection for. The specification defines the term by way of examples at page 8, however, examples are insufficient to establish the metes and bounds of a

claim. It is suggested that the claim recite the actual conditions that applicant considers to be stringent, i.e., salt concentration and temperature conditions of incubations and washes.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-3 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. The claims are directed to polynucleotides of SEQ ID NO: 1 encoding polypeptides of SEQ ID NO: 2 The instant specification puts forth that the polypeptide is useful in a screening method to determine what ligands may activate or inhibit the polypeptide and also to determine what the physiological effects of the polypeptide might be (see page 1 and 4, for example). This proposed use lacks a specific and substantial utility. It is not a specific use because any integral membrane protein could be used in exactly the same way. Further, many polypeptides are known in the art, yet the polypeptides have no known function or known ligands. Any of these orphan clones could be used in the manner described in the specification for the claimed polypeptide.

Furthermore, the proposed use of the polypeptide to screen for ligands of the polypeptide or for biologic effects of the polypeptide is not a substantial utility. A substantial utility is a

practical use which amounts to more than a starting point for further research and investigation and does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be. For example, an assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would be a practical use of the material. However, a method of treating an unspecified disease or condition with a material that has no particular correlation with a disease would not constitute a substantial utility. Basic research, such as studying the properties of the claimed product or the mechanisms in which the product is involved, does not constitute a substantial utility.

The specification puts forth that the polypeptide could be involved in any number of disparate disease states, and could therefore be used as a diagnostic (page 6 and 33, for example) or therapeutic agent (see page 7 and 18, for example). A stated belief that a correlation exists between the polypeptides and any number of diseases is not sufficient guidance to use the claimed polynucleotides to treat and/or diagnosis a particular disease; it merely defines a starting point for further research and investigation.

The specification puts forth that the polynucleotides and polypeptides could be used as tissue specific or chromosomal markers, page 10. Consistent with current examination guidelines, use as a tissue specific and/or chromosomal marker is not considered to be a substantial utility. Most every polypeptide exhibits some tissue specific pattern of expression and most every gene encoding a polypeptide is localized to some region of a chromosome.

However, without some assertion that the tissue or chromosomal localization can be used to practice a particular substantial utility, as in a marker for a particular disease state, the use of the polypeptides or polynucleotides as tissue or chromosomal marker does not constitute a substantial utility.

The specification puts forth that the polypeptide and/or polynucleotides could be used in forensic biology (page 37). However the specification does not teach that any particular nucleic acid or amino acid sequence is distinctive of any individual. While one of skill in the art would appreciate that there may exist polymorphisms in the disclosed sequences, this amounts to nothing more than an invitation to the skilled artisan to try and find such polypmorphisms if they exist.

The specification puts that the polypeptide has similarity to known taste, pheromone, calcium sensing, peptide hormone, and glutamate receptors (page 5), however the specification does not appear to assert that the polypeptide has any particular functional properties. The specification asserts that the polypeptide or polynucleotide could be used as part of a micro-array for toxicology testing, drug screening, and pharmacogenomics (see pages 11 and 14). These purposed uses are not substantial utilities because each use amounts to no more than an invitation to study the properties of the polynucleotide or polypeptides, e.g. to determine whether a compound alters the expression of the polypeptide, and then to determine what, if any, the consequence of that alteration may be, or also to determine what ligands might bind to the

polypeptide, e.g. drug screening. Such an invitation to perform research on the claimed polynucleotide is not a substantial utility.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific or substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are also rejected under 35 U.S.C. § 112 first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Furthermore, claim 1 encompasses a vast genus of polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 2, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 2; should Applicant establish a specific and substantial utility for the claimed polynucleotides, Applicant has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of

SEQ ID NO: 2, but which still retain a desired property of the polypeptide of SEQ ID NO: 2. Furthermore, Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 2 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 2 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 2 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 2. Conversely, if a protein variant of SEQ ID NO: 2 need not have a disclosed property, the specification has failed to teach how to use such a variant.

The specification has failed to provide an activity of SEQ ID NO: 2 to be used to evaluate the claimed variants for usefulness. The specification has not provided a working example of the use of a variant of the polypeptide of SEQ ID NO: 2 nor sufficient guidance so as to enable one of skill in the art to make such a variant. The specification has failed to teach which amino acids of SEQ ID NO: 2 could be modified so as to produce a polypeptide that is not identical to SEQ ID NO: 2 and yet still retain the activity of the polypeptide of SEQ ID NO: 2 - which has apparently not been disclosed.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient

guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 2 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing variants (e.g. page 8 and 19-21), this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the infinite number of variant recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a polynucleotide of SEQ ID NO: 1 and several single nucleotide sequence variants of SEQ ID NO: 1, yet it is unclear if these variations are due to errors in the sequencing of SEQ ID NO: 1 or are naturally occurring polymorphisms (see page 7, lines 27 and 28). Claim 1, however, encompasses a vast genus of polynucleotides that are not described in the specification, i.e. polynucleotides which comprise only portions of SEQ ID NO: 2, e.g. sequences from other species, mutated sequences, allelic variants, or sequences that have a recited degree of identity. The specification does not meet the written description provision of 35 U.S.C. 112, first paragraph for these sequences. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a polynucleotide, that of SEQ ID NO: 1, encoding a polypeptide with no instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A

description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence SEQ ID NO: 1, and perhaps two polymorphic variants, which are not sufficient to describe the essentially limitless genera encompassed by the claims.

The instant claims are not directed to that which is disclosed as essential to the invention, i.e. something that is homologous to the parent SEQ ID NO: 1 and has the function of the parent polynucleotide. Thus, with the exception of the of the polynucleotide of SEQ ID NO: 1 and the disclosed variants, and other polynucleotides which encode a polypeptide of SEQ ID NO: 2, the skilled artisan cannot envision encompassed multitude of variants. Therefore, only polynucleotides encoding a polypeptide of SEQ ID NO: 2, and polynucleotides *consisting* of fragments thereof, and the disclosed polynucleotide variants, or polynucleotides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/06592, ZUKER et al., February 10, 2000.

WO 00/06592 an isolated nucleic acid molecule comprising a nucleic acid sequence comprising at least 22 contiguous bases of SEQ ID NO: 1 (see attached sequence alignment).

Conclusion

12. No claims are allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

MB

June 12, 2002